Uncovering the hidden side of brain lesions

Brain lesions are areas of abnormal tissue that have been damaged due to injury or disease, which can range from being relatively harmless to life-threatening. Clinicians typically identify them as unusual dark or light spots on CT or MRI scans which are different from ordinary brain tissue.

But while conventional neuroimaging analyses can detect the location and structure of a lesion, they tell us little about the wider impact of a particular lesion on the brain's neuronal circuitry. Understanding this is crucial to being able to quantify the effects of brain damage on the whole brain, as well as exploring the effects of such lesions on a person's behavioural and cognitive abilities. This could improve our understanding of brain function, and lead to better clinical care for patients suffering from brain damage.

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And language comprehension. Upon Leborgne's death in 1861 at the age of 51, an autopsy revealed a large lesion in the part of his frontal lobe known as the posterior inferior frontal gyrus. This specific region became directly associated with our ability to produce meaningful sounds, and ever since it has remained one of the most widely studied language regions in cognitive psychology.

Through similar case studies, many other high-level cognitive processes such as attention, memory, and problem solving have become associated with different localised brain regions. However, while this may appear to be a logical way to determine how the brain operates, some scientists have long suspected that this has painted a picture of the brain which is rather too simplistic.

The problem is that different neurological processes are not purely confined to individual specialised regions. Instead, many of the brain's estimated 100 billion neurons form connections between very distant parts of the brain, and it may be that the real impact of brain lesions is through interrupting these complex networks. Disconnections in the brain's circuitry could have functional and anatomical consequences for brain regions located a long distance away from the lesion. For example, if certain regions are no longer receiving a signal because of a lesion, they can no longer take part in the function they were involved in. This can result in many of the neurons in these regions becoming subject to atrophy, as well as reductions in dendrite and synapse density, and ultimately neuronal death through a programmed cellular mechanism called apoptosis. Because of this, lesions may well have a wider impact in the brain which extends far beyond the visible damage apparent on imaging scans.

However, there are relatively few technologies available which researchers can utilise to capture and analyze the long-range effects resulting from lesion-induced brain disconnections. Scientists have previously attempted to use a variety of 3D modelling and image analysis techniques for exploring the nonlocal effects of lesions. However few of these methods are open-access, making them inaccessible to many scientists. In addition, much of the research conducted so far has lacked a standardised way of determining what these techniques are actually measuring, and how they should

**HOW DO BRAIN LESIONS IMPACT BRAIN FUNCTION?**

Traditionally, if a patient has a lesion in a certain part of their brain, and displays a particular set of symptoms, such as reduced spatial awareness or impaired language production, neurologists deduce that these symptoms are a direct result of functional changes in the visibly damaged area.

Studying these patients and what happens when damage occurs to individual brain areas has improved our overall understanding of the brain in healthy individuals over the past two centuries. One famous example is the case of Louis Leborgne, who ultimately spent 21 years in Bicêtre Hospital, Paris, having lost the ability to produce coherent speech despite retaining many other faculties such as intelligence.

**Phineas Gage (1823-1869), survived a terrible incident in which his left frontal lobe was blown away by a tampering iron bar. As a result, Gage's personality changed and he became the index case of acquired 'sociopathy'. Analyses of the neuronal circuitry impaired by the lesion revealed that areas outside the frontal lobe were also disconnected (shaded in red (right panel)). Importantly, these areas are classically involved in social cognition including decision-making and emotions (right panel). In sum, these areas may well have contributed to the change of personality shown in Phineas Gage as much as the areas damaged by the passage of the tampering bar.**

**Example of the pathway, highways of the brain, connecting the front with the posterior part of the brain.**
BCBtoolkit allows scientists to discern the natural history of events which occurred in the brain following a lesion.

These programs measure the brain circuitry, estimate the subsequent changes within these circuits which have been caused by a particular lesion and use this information to deduce which changes are contributing to the patient's symptoms.

This is important as studies have suggested that the extent of a patient's ability to recover from a lesion depends on the exact patterns of change induced within their brain circuitry. For example, one 2014 study of 16 stroke patients found that the ability of these patients to recover from speech impairment following a stroke in the left brain hemisphere, depended on the number of connections remaining between the equivalent of Broca’s area and Wernicke’s area – two of the most important regions for language use – in the right hemisphere.

To prove that BCBtoolkit could be clinically useful for studying patients with brain lesions, Thiebaut de Schottan’s lab have used the package to study the brain connections of 37 patients with frontal lobe lesions resulting from a stroke, infection, hematoma or surgical removal of a brain tumour or of an epileptogenic area.

Initially, they applied the software to map the patient's lesions onto virtual brain scans of hundreds of healthy individuals, showing every neural connection going to and from the damaged areas. These representations enabled them to visualise which brain regions had been structurally disconnected by the lesions.

To understand the link between these disconnections and the patients' symptoms, they then conducted various neuropsychological assessments on each patient, such as category fluency tests where patients undergo different exercises such as naming as many animals as they can in two minutes.

The results of these tests suggested that the patients were suffering from cognitive problems such as impaired language, working memory and verbal fluency, related to brain disconnections in major networks associated with processes such as executive function, as well as language and semantic production.

Having identified the precise regions affected by brain disconnections in these patients, the researchers used BCBtoolkit to analyse data collected on these regions from MRI scans. By measuring cortical thickness, they were able to estimate the total neural loss in these areas. This provided further evidence that many of the patients' cognitive impairments were at least partially linked to a loss of cortical neurons in regions located far away from the original lesion.

“For the very first time, using our program, we were able to measure disconnections within the brain of a group of patients and associate neuropsychological deficit with disconnection,” Michel Thiebaut de Schotten explained. “We hope to better understand the brain's underlying mechanisms and increase symptom predictability in patients with brain lesions.”

THE FUTURE

Patients with brain lesions have always provided researchers with a unique opportunity to understand the functioning of the human mind. Through BCBtoolkit, scientists working in this field now have, for the first time, a scientifically validated set of methods for capturing the impact of brain damage on the whole brain.

This allows scientists to try and discern the natural history of events which occurred in the brain following a lesion, as well as exploring the relationship between these damaged areas and behavioural and cognitive symptoms.

But while this is currently just a research tool, in future it could have considerable clinical benefit for patients themselves. Every year, more than 2 million people across Europe suffer a stroke, often resulting in persistent lesions which affect their personality, quality of life and prevent them from being able to return to work. As a result, there is a considerable clinical need for diagnostic technologies which allow neurologists to inform these patients and their families in a timely manner, the extent to which their symptoms will resolve.

However, despite decades of scientific studies describing the symptoms resulting from different lesions, neurologists still typically have little idea of how well a patient will recover from a particular lesion. The only option available is to simply observe how that patient progresses over the course of weeks and months.

But through BCBtoolkit and other similar packages being developed for lesion-symptom mapping, this could soon change. By using these techniques to study the impact of different sized lesions in different locations in the brain, neurologists will be able to stratify patient populations more accurately than ever before. This will allow them to predict the patients who are more likely to make a partial or full recovery, enabling them to act much sooner with treatment and rehabilitation plans for patients who have sustained lasting damage. Such knowledge will allow patients and their families to begin making appropriate arrangements with employers and in many countries, health insurance providers, at a much earlier stage than usual, reducing the burden and stress associated with stroke.

A NEW METHOD FOR EXPLORING THE IMPACT OF BRAIN LESIONS

Dr Michel Thiebaut de Schotten – principal investigator at the Brain Connectivity and Behaviour Lab at the ICM Institute in Paris – and colleagues have developed a new open-access software package called BCBtoolkit which consists of a set of programs for analysing the long-range effects of brain disconnections.
Research Objectives

Dr Michel Thiebaut de Schotten and colleagues at the ICM Institute in Paris have developed a software package called BCBtoolkit which can help researchers and clinicians understand the effects of brain damage on brain connections. In future, this could help evolve our understanding of high-level cognitive functions, as well as helping neurologists to predict whether a patient will recover or not from a stroke or other brain injuries.

References


Behind the Research

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Bio
With over twelve years’ experience in neuropsychology and brain connectivity neuroimaging, Dr Thiebaut de Schotten benefits from an established scientific track record. His research work has been on the elaboration of new methods and has led to the reporting of novel observations from which new theories on the functioning of the brain were derived.

Funding
• Centre National de la Recherche Scientifique (CNRS)
• Agence Nationale de la Recherche (grant ANR-13- JSV4- 0001-01)

Collaborators
• Chris Foulon, PhD
• Emmanuelle Volle, Researcher

References


Personal Response

Can you describe how neurologists could use BCBtoolkit to predict how well a patient will recover from a particular brain lesion?

Neurologists can use our software to estimate the extent of the brain disconnection. The more the disconnection of the brain, the less likely the patient will recover. We are now implementing new open tools which will not only decode the patient symptoms but also provide a tailor-made indication of potential recovery for any stroke patient no matter where their lesion occurs. We plan to apply the same technology in the future for the planning of brain surgery and the early identification and the stratification of neurodegenerative disorders such as Alzheimer.

What are your future plans for research in this area?

Future plans include understanding how the brain can change its functioning to compensate for impairment and how we can help the brain to better achieve these compensatory changes. Additionally, we wish to understand what the differences are between patients in term of anatomy and functioning of the brain that drives their differences in recovery.